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REMARKS/ARGUMENTS

Item 2. Amendments

The Examiner notes that claims 6-10 were missing from one version of the amendment filed 4/3/2006. The deletion of pages containing claims 6-10 was due to a FAX machine error. Applicants respectfully direct the Examiner's attention to the corrected version of the amendment filed a couple of minutes later on 4/3/2006. Applicants note that the corrected version is present on the PAIR system Image File Wrapper. Applicants also note that claims 9 and 10 were amended in the amendment filed on 4/3/2006.

Item 3. Claims 4-5, 7 and 42-43 were rejected under 35 U.S.C. 112, second paragraph.

Claims 4 and 5 have been amended to recite said "at least one heteroduplex" of Claim 1 providing proper antecedent basis, hence it is requested that this rejection be withdrawn.

Claim 7 has been rewritten as an independent claim for additional clarity. Applicants respectfully request that this rejection be withdrawn.

Claims 42-43 were rejected as indefinite over the recitation of the phrase "effective amount". This rejection is respectfully traversed. The phrase "effective amount" is defined in paragraph [0053] on p. 11 of the specification. Specific examples of an effective amount include Example 1 wherein a dilution series of CEL I enzyme is taught for an effective amount of strand cleavage activity. Additional examples include Example 2 wherein effective amounts of CEL I, T4 DNA polymerase and T4 ligase are taught (paragraph [00193]), and paragraph [00194] teaching a matrix experiment defining effective amounts of activities under various incubation temperatures. Paragraph [00195] teaches effective amounts of other enzyme activities. Example 3 in paragraph [00197] teaches effective amounts of the reaction activities in a scaled-up reaction. Example 6 teaches effective amounts of activities by examining a matrix of three different CEL I concentrations versus two concentrations of T4 DNA polymerase. Example 8 teaches the effective amounts of T7

DNA polymerase that can substitute for T4 DNA polymerase in the reaction. Examples 10, 12, 13, 14, 15 and 16 also teach effective amounts of activities. In addition, instructions as to effective amounts can standardly be found in the product literature supplied by manufacturers of commercially available enzymes. Applicants submit that these teachings give sufficient guidance as to an "effective amount" of the activities necessary to practice the invention as claimed, and respectfully request that this rejection be withdrawn.

Item 4. Claims 1-2, 4 and 6-8 were rejected under 35 U.S.C. 102(b) as being anticipated by Chirikjian et al. This rejection is respectfully traversed. Chirikjian et al. teach methods for point mutation detection and for site-directed mutagenesis. Their output molecules are either a cleaved polynucleotide (in the case of mismatch detection, e.g. pp. 4-6) or a polynucleotide that corresponds to the sequence of either the target polynucleotide parent or the mutagenic oligonucleotide parent. The objective of Chirikjian et al. is essentially to convert one parent sequence to the other parent sequence. Chirikjian et al. do not teach the generation of polynucleotide strands with different nucleotide sequences from the parent polynucleotides as required in the instant invention. Chirikjian et al. are not motivated to make variant sequences, as they know beforehand the sequence they wish to generate. The objective of the instant invention is to generate a population of sequence variants that can be screened for a desired functional property. Such an objective is not taught or contemplated by Chirikjian et al. As Chirikjian et al. do not anticipate the instant invention, this rejection should be withdrawn.

Item 5. Claim 5 was rejected under 35 U.S.C. 103(a) over Chirikjian et al. in view of Wetmur. This rejection is respectfully traversed. Wetmur does not compensate for the deficiencies of Chirikjian et al. as described above. Wetmur teaches a method of mismatch detection (like Chirikjian et al.), but applied to a whole genome. Wetmur does not teach or contemplate a method of preparing variant polynucleotides having a nucleotide sequence different from the parents. The examiner contends one would be motivated to apply the technique of Wetmur to the method of Chirikjian et al. in order to detect differences between two genomes which can then be applied towards genome mapping and or cloning genes based on sequence differences or similarities between the two genomes. However, applying Wetmur to Chirikjian et al. does not result in the instant invention. The instant invention as claimed does not seek to detect differences between two genomes, but rather to reassort sequence variation between strands of a heteroduplex resulting in polynucleotide variants having a different nucleotide sequence from the parents. Both Chirikjian et al. and Wetmur are interested in mismatch detection, and are not motivated to reassort sequence variation. According, this rejection should be withdrawn.

Item 6. Claims 9-12 and 42-43 are rejected under 35 U.S.C. 103(a) over Chirikjian in view of Arnold. This rejection is respectfully traversed. The deficiencies of Chirikjian et al. are noted above. Regarding Claims 9 and 43, Chirikjian et al. do not teach screening or selecting a population of variants for a desired functional property since they do not even generate a population of variants, but rather generate a sequence corresponding to one or the other parents. Since Chirikjian et al. generate no population of variants, there is no motivation to apply the screening or selecting technique of Arnold et al. to the method of Chirikjian et al. According, this rejection should be withdrawn.

Regarding Claim 10, Chirikjian et al. is not motivated to repeat their process since the site-directed mutagenesis process gives them the desired sequence in the first attempt. One might be motivated to repeat the method of Chirikjian et al. to make a second site-directed mutation, but this still does not result in the instant invention, as the output molecules will still reflect the sequences of either the target polynucleotide or the mutagenic oligonucleotide. No population of variants is generated. Accordingly, this rejection should be withdrawn.

Regarding Claims 11 and 12, again, since Chirikjian et al. do not generate a population of variants, there are no variants to convert to RNA before screening. Accordingly, this rejection should be withdrawn.

Regarding Claim 42, the deficiencies of Chirikjian et al. have been noted above. Adding the *in vitro* cell extracts of Arnold et al. adds nothing to Chirikjian et al. in terms of generating a population of sequence variants. The conversion of the heteroduplex of Chirikjian et al. will still result in an output polynucleotide with a sequence corresponding to one or the other parent polynucleotide. Hence, it is respectfully requested that this rejection be withdrawn.

Items 7-10. Provisional Double Patenting. Claims 1-2, 4-12, and 42-43 are provisionally rejected over the claims of several co-pending applications. Applicants request that resolution of provisional obviousness-type double patenting matters be postponed until patentable subject matter is identified in the instant application. Such rejections could potentially be resolved, for example, *via* a terminal disclaimer.

Claims 1, 2, 4-12, 42 and 43 are now pending in the application. In view of the amendments and comments above, the rejections have been overcome. Reconsideration, withdrawal of the rejections and early indication of allowance are respectfully requested. If any issues remain, the examiner is encouraged to call the undersigned for prompt resolution.

If needed, Applicants petition for an extension of time under the provisions of 37 CFR 1.136(a) for sufficient time to accept this response. The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,

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